2. RELEVANCE TO PUBLIC HEALTH

The primary purpose of this chapter is to provide a summary of the health effects of copper based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for the primary health effects of copper. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

For a more detailed discussion of the toxicity of copper and the potential for human exposure, please see Chapters 3 and 6, respectively.

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO COPPER IN THE UNITED STATES

Copper is a metallic element that occurs naturally as the free metal. Most copper compounds occur in +1 Cu(I) and +2 Cu(II) valence states. Copper is primarily used as a metal or an alloy (e.g., brass, bronze, gun metal). Copper sulfate is used as a fungicide, algicide, and nutritional supplement. Copper particulates are released into the atmosphere by windblown dust; volcanic eruptions; and anthropogenic sources, primarily copper smelters and ore processing facilities. Copper particles in the atmosphere will settle out or be removed by precipitation. The mean concentration of copper in ambient air in the United States is 5–200 ng/m^3. Copper is released into waterways by natural weathering of soil and rocks, disturbances in soil, or anthropogenic sources (e.g., effluent from sewage treatment plants). Copper concentrations in drinking water vary widely as a result of variations in pH and hardness of the water supply; the levels range from a few ppbs to 10 ppm. The mean concentration of copper in soil in the United States ranges from 14 to 41 mg/kg. The daily intake of copper from food is 1.0–1.3 mg/day for adults.

The general population is exposed to copper through inhalation, consumption of food and water, and dermal contact with air, water, or soil that contains copper. The primary source of copper is the diet; however, the amount of copper in the diet does not usually exceed the dietary requirements for copper. Drinking water is the primary source of excess copper. Populations living near sources of copper emissions, such as copper smelters and refineries and workers in these and other industries may also be exposed to high levels of copper in dust by inhalation. Copper has been identified in at least 884 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA NPL.

2.2 SUMMARY OF HEALTH EFFECTS

Copper is an essential nutrient that is incorporated into a number of metalloenzymes involved in hemoglobin formation, carbohydrate metabolism, catecholamine biosynthesis, and cross-linking of collagen, elastin, and hair keratin. The copper-dependent enzymes, some of which are cytochrome c oxidase, superoxide dismutase, ferroxidases, monoamine oxidase, and dopamine β-monooxygenase, function to reduce molecular oxygen. Symptoms associated with copper deficiency in humans include normocytic, hypochromic anemia, leukopenia, and osteoporosis; copper deficiency is rarely observed in the U.S. general population. In the United States, the median intake of copper from food is 0.93–1.3 mg/day for adults (0.013–0.019 mg Cu/kg/day using a 70-kg reference body weight). A recommended dietary allowance (RDA) of 0.9 mg/day (0.013 mg/kg/day) has recently been established .

Copper is readily absorbed from the stomach and small intestine; after nutritional requirements are met, there are several mechanisms that prevent copper overload. Excess copper absorbed into gastrointestinal mucosal cells is bound to the metal binding protein metallothionein. This bound copper is excreted when the cell is sloughed off. Copper that eludes the intestinal barrier can be stored in the liver or incorporated into bile and excreted in the feces. Although copper homeostasis plays an important role in the prevention of copper toxicity, exposure to excessive levels of copper can result in a number of adverse health effects including liver and kidney damage, anemia, immunotoxicity, and developmental toxicity. Many of these effects are consistent with oxidative damage to membranes or macromolecules. Copper can bind to the sulfhydryl groups of several enzymes, such as glucose-6-phosphatase and glutathione reductase, thus interfering with their protection of cells from free radical damage.

One of the most commonly reported adverse health effect of copper is gastrointestinal distress. Vomiting, nausea, and abdominal pain, usually occurring shortly after drinking beverages that were stored in a copper or untinned brass container or first draw water (water that sat in the pipe overnight) . The observed effects are not usually persistent or associated with other health effects. Animal studies have also reported gastrointestinal effects (hyperplasia of forestomach mucosa) following ingestion of copper sulfate in the diet. Copper is also irritating to the respiratory tract. Coughing, sneezing, runny nose, pulmonary fibrosis, and increased vascularity of the nasal mucosa have been reported in workers exposed to copper dust.

The liver is also a sensitive target of toxicity. Liver damage (necrosis, fibrosis, abnormal biomarkers of liver damage) have been reported in individuals ingesting lethal doses of copper sulfate. Liver effects

have also been observed in individuals diagnosed with Wilson's disease, Indian childhood cirrhosis, or idiopathic copper toxicosis. These syndromes are genetic disorders that result in an accumulation of copper in the liver; the latter two syndromes are associated with excessive copper exposure. Inflammation, necrosis, and altered serum marker of liver damage have been observed in rats fed diets with copper sulfate levels that are at least 100 times higher than the nutritional requirement. Damage to the proximal convoluted tubules of the kidney have also been observed in rats. The liver and kidney effects usually occur at similar dose levels; however, the latency period for the kidney effects is longer than for the liver effects.

There is some evidence from animal studies to suggest that exposure to airborne copper or high levels of copper in drinking water can damage the immune system. Impaired cell-mediated and humoral-mediated immune function have been observed in mice. Studies in rats, mice, and mink suggest that exposure to high level of copper in the diet can result in decreased embryo and fetal growth.

The carcinogenicity of copper has not been adequately studied. An increase in cancer risk has been found among copper smelters; however, the increased risk has been attributed to concomitant exposure to arsenic. Increased lung and stomach cancer risks have also been found in copper miners. However, a high occurrence of smoking and exposure to radioactivity, silica, iron, and arsenic preclude associating the risk with copper exposure. Animal studies have not found increased cancer risks in orally exposed rats or mice. IARC has classified copper 8-hydroxyquinoline in Group 3, unclassifiable as to carcinogenicity in humans and EPA has classified copper in Group D, not classifiable as to human carcinogenicity

A more detailed discussion of the critical targets of copper toxicity, the gastrointestinal tract and the liver, follows.

Gastrointestinal Effects. The available human and animal data suggest that the gastrointestinal tract is a sensitive target of toxicity. There are numerous reports of nausea, vomiting, and abdominal pain immediately after ingesting beverages contaminated with copper; these effects are not usually persistent. Nausea, vomiting, and/or abdominal pain have been observed following exposure to a single dose of copper sulfate of 4 mg/L and higher, which is equivalent to a dose of 0.011 mg/kg. These symptoms were also reported in adults drinking water containing >3 mg/L copper sulfate (0.0731 mg Cu/kg/day) for 1–2 weeks. Similar gastrointestinal effects were observed in adults ingesting copper oxide. Although gastrointestinal irritation may play a role in the observed gastrointestinal effects, data from ferrets and

monkeys suggest that vagal afferent fibers and 5-HT_3 and 5-HT_4 receptors are involved in copper-induced emesis.

Hepatic Effects. In humans, copper-induced hepatic damage is dependent on several factors including genetics, age, and copper intake. Liver damage is rarely reported in adults; the few reported cases of liver damage (centrilobular necrosis, jaundice, and increased aspartate aminotransferase activity) have been associated with intentional ingestion of a lethal dose of copper sulfate. In infants and children, reported liver effects are usually manifested in one of three syndromes: Wilson's disease, Indian childhood cirrhosis, and idiopathic copper toxicosis. Wilson's disease is an autosomal recessive genetic disorder associated with impaired copper metabolism. Although very high levels of copper are found in the liver, dietary exposure to higher than normal levels of copper does not appear to be necessary for the manifestation of liver damage. There is strong evidence that Indian childhood cirrhosis and idiopathic copper toxicosis are also caused by a genetic defect that is transmitted in an autosomal recessive mode. However, unlike Wilson's disease, manifestation of the disease is associated with exposure to unusually high levels of dietary copper from milk stored in copper or brass containers or from drinking water. The clinical age of onset is usually between 6 months and 5 years, and the observed liver effects include pericellular fibrosis, abnormal biochemical markers of liver damage (e.g., increased serum aspartate aminotransferase and alkaline phosphatase activities and serum bilirubin levels), and very high levels of copper in the liver. In general, the potential hepatotoxicity of copper has not been extensively investigated in healthy humans. Two studies have established no effect levels of 0.14 and 0.315 mg Cu/kg/day in adults and infants, respectively; both studies used serum chemistry biomarkers (e.g., alanine aminotransferase, aspartate aminotransferase) to assess liver damage.

Adverse liver effects have been observed in rats exposed to dietary copper levels that were more than 100 times higher than the nutritional requirement. The liver effects included inflammation, necrosis, and abnormal serum chemistry markers of liver damage. Rats appear to develop a tolerance to copper doses of 180–<550 mg Cu/kg/day. Tolerance is defined as "the ability to endure the continued or increasing administration of a toxicant and the capacity to exhibit less response to a test dose than previous". As the levels of hepatic copper increase, so does the severity of the damage until peak copper levels are reached. After about 3–5 weeks of exposure, the copper levels begin to decline and are maintained at a steady level for the remainder of the exposure period. When the hepatic levels decline, regeneration of hepatic tissue is observed, and continued exposure or exposure to higher doses does not result in more tissue damage. The decline in hepatic copper levels and regeneration of damaged tissue occurs early at higher doses. At

doses >550 mg Cu/kg/day, the liver becomes permanently overloaded and chronic hepatitis develops. Regeneration was also not seen at doses of 140 mg Cu/kg/day and lower.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

The available data on the toxicity of inhaled copper were considered inadequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs. Data on the inhaled toxicity of copper in humans following acute-duration exposure are limited to a report of workers developing metal fume fever while cutting brass pipe with an electric cutting tool in a poorly ventilated area (Armstrong et al. 1983); exposure levels were not reported. Respiratory effects and impaired immune function have been observed in mice following a single exposure to 3.3 mg Cu/m^3 as copper sulfate or repeated exposure to 0.12–0.13 mg Cu/m^3 as copper sulfate (Drummond et al. 1986). The Drummond et al. (1986) study was not used to derive an acute-duration inhalation MRL because a small number of animals was tested (four per group) and a limited number of end points (respiratory tract and immune function) were examined. Intermediate-duration data are limited to studies by Johansson et al. (1983, 1984), which did not find any histological alterations in the lungs or functional or morphological alterations in alveolar macrophages of rabbits exposed to copper chloride. As with the acute-duration data, the limited number of end points examined preclude deriving an intermediate-duration inhalation MRL. The chronic-duration database for copper consists of two occupational exposure studies reporting respiratory (Askergren and Mellgren 1975; Suciu et al. 1981) and gastrointestinal (Suciu et al. 1981) irritation, hepatic effects (Suciu et al. 1981), and possible neurological and reproductive effects (Suciu et al. 1981). Chronic-duration inhalation MRLs cannot be derived from these studies due to poor exposure characterization and/or lack of controls.

Oral MRLs

- An MRL of 0.02 mg/kg/day has been derived for acute-duration oral exposure (1–14 days) to copper.

The available human and animal acute-duration studies strongly suggest that the gastrointestinal tract is the most sensitive target of copper toxicity. Numerous studies have reported nausea, vomiting, and abdominal pain immediately following ingestion of copper-contaminated water or other beverages. In studies involving a single exposure to copper, adverse gastrointestinal effects (nausea, vomiting, abdominal pain, and/or diarrhea) have been observed at doses of 0.011–0.08 mg Cu/kg (Araya et al. 2001;

Gotteland et al. 2001; Nicholas and Brist 1968; Olivares et al. 2001); the study by Olivares et al. (2001) reported a no effect level of 0.0057 mg/kg. Several studies have examined the gastrointestinal tract effects following repeated exposure to elevated levels of copper in drinking water. In a 2-week study, 60 women were given copper sulfate containing water to be used for drinking and cooking purposes. An increased occurrence of nausea, vomiting, and/or abdominal pain was observed when the women were given 5 mg/L copper sulfate (0.0731 mg Cu/kg/day) (Pizarro et al. 1999). No adverse effects were noted at copper concentrations of 1 or 3 mg/L (0.0006 or 0.0272 mg Cu/kg/day). Nausea, vomiting, and/or abdominal pain were also reported by women ingesting water containing 5 mg/L (0.1 mg Cu/kg/day) as copper sulfate or copper oxide for 1 week (Pizarro et al. 2001). Animal studies support the identification of the gastrointestinal tract as a sensitive target of toxicity. Hyperplasia of the forestomach mucosa was observed in rats exposed to 44 mg Cu/kg/day as copper sulfate in the diet (NTP 1993) and in mice exposed to 197 mg Cu/kg/day as copper sulfate in the diet (NTP 1993). At higher doses, liver and kidney damage have been observed (Haywood 1980; Haywood and Comerford 1980; Haywood et al. 1985b; NTP 1993).

An acute-duration oral MRL of 0.02 mg Cu/kg/day was derived for copper based on gastrointestinal effects using the data from the Pizarro et al. (1999) study. To estimate total copper exposure, the concentration of copper in the drinking water (0.0272 mg Cu/kg/day) was added to the reported average dietary copper intake (0.0266 mg Cu/kg/day). The total copper exposure level of 0.0538 mg Cu/kg/day was considered a no-observed-adverse-effect-level (NOAEL) for gastrointestinal effects. The NOAEL was divided by an uncertainty factor of 3 (to account for human variability) to yield an acute-duration oral MRL of 0.02 mg Cu/kg/day. The acute-duration MRL, which accounts for dietary exposure as well as environmental contamination, is approximately 2 times higher than the RDA and is slightly higher than the upper end of the range of typical dietary intakes.

- The acute-duration oral MRL of 0.02 mg Cu/kg/day has been adopted as the intermediate-duration oral MRL.

There are limited data on the intermediate-duration toxicity of copper in humans. In a study by Pratt et al. (1985), a group of seven adults were administered 10 mg Cu/day (0.14 mg Cu/kg/day) as copper gluconate in a capsule for 12 weeks. No significant alterations in serum markers of liver damage (cholesterol and triglyceride levels and aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, and lactate dehydrogenase activities) were found. Similarly, no alterations in total bilirubin, serum alanine aminotransferase, serum aspartate aminotransferase, or gamma glutamyl transferase were observed in infants exposed to 0.315 mg Cu/kg/day for 9 months (Olivares et al. 1998). Neither study

reported significant alterations in the occurrence of gastrointestinal disturbances, although the high dropout rate observed in the copper-exposed infants may have been related to gastrointestinal effects. Severe liver damage (pericellular fibrosis, increased serum aminotransferase and alkaline phosphatase activities) has been observed in children with a genetic susceptibility to high levels of copper in the liver. Numerous studies in rats support the identification of the liver as a critical target of toxicity following intermediate-duration oral exposure. Inflammation, necrosis, and increased alanine and aspartate aminotransferases activities have been reported at exposure levels of 16 mg Cu/kg/day as copper sulfate in the diet (Haywood 1980, 1985; Haywood and Comerford 1980; Haywood and Loughran 1985; Haywood et al. 1985a; NTP 1993). No liver effects where observed at 8 mg Cu/kg/day (NTP 1993). The Pratt et al. (1985) and Olivares et al. (1998) studies provide suggestive evidence that liver effects are not likely to occur at lower doses than gastrointestinal effects following intermediate-duration oral exposure.

The database on the chronic oral toxicity of copper is inadequate for derivation of a MRL. Massie and Aiello (1984) reported a 15% decrease in the lifespan in mice exposed to 4.2 mg Cu/kg/day as copper gluconate in drinking water.